Prevention and Treatment of Recurrent *Clostridioides difficile* Infection

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### Learning Objectives

- Discuss the epidemiology of recurrent *Clostridioides difficile* infection (CDI).
- Identify special populations at risk for recurrent CDI in practice.
- Summarize current and emerging pharmacologic and non-pharmacologic therapies for the prevention and treatment of recurrent CDI.
- Develop an interprofessional treatment plan for recurrent CDI for special populations.

### Abbreviations

- AML- acute myeloid leukemia
- BID- twice daily
- CDC- Centers for Disease Control and Prevention
- EIA- enzyme-linked immunosorbent assay
- FDX- fidaxomicin
- FMT- fecal microbiota transplant
- GERD- gastroesophageal reflux disease
- GDH- glutamate dehydrogenase
- HSCT- hematopoietic stem cell transplantation
- IBD- inflammatory bowel disease
- IV- intravenous
- MTZ- metronidazole
- NAAT- nucleic acid amplification test
- PMH- past medical history
- QID- four times daily
- RCT- randomized controlled trial
- rCDI- recurrent CDI
- Scr- serum creatinine
- SOC- standard of care
- UTI- urinary tract infection
- VAN- vancomycin
- WBC- white blood cell count
The Epidemiology of Recurrent *Clostridioides difficile* Infections

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**Etiology of Healthcare-Associated Infection**

- *E. coli*, 10%
- *S. aureus*, 11%
- *C. difficile*, 15%
- Candida spp., 6%
- Enterococcus spp., 5%
- Enterobacter spp., 5%
- Pseudomonas spp., 5%
- Klebsiella spp., 5%
- Other gram negatives, 12%
- Coagulase-negative Staphylococcus spp., 4%
- Streptococcus spp., 5%
- Other gram positives, 3%
- Unspecified yeast, 1%
- Mold, 1%
- Virus, 1%
- No pathogen reported, 30%

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**Clostridioides difficile: A history**

- 1893 • Pseudomembranous colitis described
- 1935 • First described as *Bacillus difficilis* by Hall and O’Toole
- 1978 • *C. difficile* associated with antibiotic-associated diarrhea
- 2002 • *C. difficile* incidence, morbidity, and mortality increase
- 2013 • CDC labels *C. difficile* as threat level Urgent
- 2019 • CDC reaffirms *C. difficile* as threat level Urgent

**What is Clostridioides difficile?**

- Formerly known as *Clostridium difficile*
  - Nomenclature changed in 2018
- Toxin-producing
  - Toxin A (TcdA)
  - Toxin B (TcdB)
  - Binary Toxin (CDT)
- Spore-forming
- Gram-positive, anaerobic bacilli

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**CDC 2013**

\textit{C. difficile}, Threat Level Urgent

![Image of C. difficile threat level urgent]


**CDC 2019**

\textit{C. difficile}, Threat Level Urgent

![Image of C. difficile threat level urgent]

C. difficile Infection

- CDI symptoms range from asymptomatic carriage to mild diarrhea to fulminant colitis and death
- CDI is defined as the presence of symptoms plus:
  - A positive stool test for *C. difficile* toxin B or detection of toxigenic *C. difficile* by PCR
  - OR
  - Colonoscopy or histopathologic findings revealing pseudomembranous colitis

Diagnosis of CDI

- Symptoms
  - Diarrhea: Defined as three or more unformed stools over 24 hours
- Diagnostic tests
  - Toxin A/B EIA
  - GDH
  - NAAT
  - Multistep algorithms
    - GDH/Toxin EIA Plus NAAT
    - NAAT Plus Toxin EIA
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### Current *C. difficile* Testing Methods

<table>
<thead>
<tr>
<th>Diagnostic Test</th>
<th>Testing Target</th>
<th>NPV</th>
<th>PPV</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>GDH/Toxin EIA + NAAT (MST)</td>
<td>1) Glutamate dehydrogenase 2) Presence of Toxin A or B 3) Genes that code for toxin production</td>
<td>99%</td>
<td>90%</td>
<td>1) Test for GDH and Toxin EIA. - If both positive, confirms CDI. 2) Complete NAAT if GDH and Toxin EIA results are discordant - If NAAT positive, confirms likely CDI</td>
</tr>
<tr>
<td>NAAT</td>
<td>1) Genes that code for toxin production</td>
<td>99%</td>
<td>92%</td>
<td>1) Does not discriminate between infection and colonization. 2) Overdiagnosis of CDI</td>
</tr>
<tr>
<td>NAAT + Toxin EIA</td>
<td>1) Genes that code for Toxin production 2) Presence of Toxin</td>
<td>99%</td>
<td>90%</td>
<td>1) Test for <em>C. difficile</em> NAAT 2) If NAAT positive, Toxin EIA test completed 3) Positive Toxin EIA confirms likely CDI - Negative Toxin EIA, does not exclude CDI and requires clinical assessment</td>
</tr>
</tbody>
</table>


### CDI Epidemiologic Categories

- 453,000 incident cases (100%)
- 64.7% healthcare-associated CDI (HA-CDI)
  - 37% hospital-onset
  - 36% LTCF-onset

- 35.3% community-associated CDI (CA-CDI)
  - 82% with outpatient healthcare exposure
  - 28% community-onset
  - 18% other

- 94% of all CDI cases had a recent healthcare exposure

LTCF = long-term care facilities


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### CDI Epidemiology

![Graph showing CDI incidence in the U.S. from 2012 to 2016: CA-CDI, HA-CDI, and All CDI estimated incidence.](image)


### Risk Factors for CDI

- Immune compromise
- Antibiotic use
- Hospitalization, residence in nursing home or rehabilitation facility
- Age >65 years

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**CDI Pathogenesis**

- Initial cure
- Recovery and restoration of colonization resistance
- Relapse or recurrence
- + CDI treatment (antibiotics)
- Dysbiosis
- + ingestion of *C. difficile* spores
- + toxin production
- Germination and growth
- Healthy microbiome


**Antibiotics as a Risk Factor for CDI**

- Highest risk of CDI (7- to 10-fold increase) during and in the first month following antibiotic exposure
  - Increased risk seen **up to 3 months** after cessation of antibiotic therapy
- Dose-dependent increases in CDI risk associated with:
  - Increasing cumulative antibiotic dose
  - Increasing number of antibiotics
  - Increasing number of days of antibiotic exposure


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### CDI Pathogenesis

- **Initial cure**
- **Relapse or recurrence**
- **Recovery and restoration of colonization resistance**

![CDI Pathogenesis Diagram](image)

**CDI Pathogenesis**

- Healthy microbiome
- Dysbiosis
- + ingestion of *C. difficile* spores
- Germination and growth
- + toxin production
- + antibiotics


### Route of Transmission

- **Ingestion of *C. difficile* spores via fecal-oral route:**
  - Person-to-person transmission (hands of healthcare personnel)
  - Environmental contamination with *C. difficile* spores
- **Healthcare facility transmission**
  - Being placed in a hospital room where the previous occupant had CDI increases risk
    - Only accounts for 10% of CDI
  - Asymptomatic carriers can transmit spores leading to infection within a hospital
    - 29% of CDI related to asymptomatic carriers, and 30% related to symptomatic patients

Healthcare association with CDI

- The prevalence of asymptomatic colonization with *C. difficile* is 3 – 26% in hospitalized adults
  - In elderly patients in LTCFs the asymptomatic colonization is 5-7%
- The prevalence of asymptomatic *C. difficile* carriage in adults without recent healthcare facility exposure is <2%
- A meta-analysis pooling 19 studies revealed the colonization rate at hospital admission was 8.1% with the main risk factor being previous hospitalization


CDI Pathogenesis

[Diagram showing the process of CDI pathogenesis]
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**Recurrent CDI**

- New CDI symptoms after resolution of symptoms with a positive test for *C. difficile* within 2-8 weeks
  - 10 – 30% of all patients with first episode CDI diagnosis suffer from recurrent disease
  - Risk increases with each successive recurrence
- Recurrence rate in CA-CDI is 9.7 cases per 100,000 people
- Recurrence rate in HA-CDI is 12 cases per 100,000 people
- Risk of mortality increases by 33% with recurrent CDI at 180 days


**Cycle of Recurrence**

- Sustained Cure 75%
- Recurrence 25%
- Recur 40%
- Cure 60%

- Risk Factors
  - Concomitant antibiotic administration
  - Increasingly severe underlying disease
  - Multiple recurrences
  - Advancing age
  - Hematologic malignancy

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**Burden of CDI in the U.S.**

- *C. difficile* responsible for ~500,000 *infections* annually
  - 83,000 1st recurrences
- Associated with 20,500 in-hospital CDI-associated deaths annually
- Associated with 29,000 30-day CDI-associated deaths annually
- Overall annual costs estimated at $5.4 billion in U.S.
  - $4.7 billion (86.7%) incurred in healthcare settings
    - CDI-attributable costs $3,427–$9,960/episode for acute care hospitals
  - $725 million (13.3%) incurred in the community


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**CDI Burden**

- 365,200 incident cases (100%)
- 53.4% Healthcare-Associated CDI
  - 20% First Recurrence
  - 50% Total Hospitalized
  - 9% In-hospital Mortality
- 46.6% Community-Associated CDI
  - 18% First Recurrence
  - 41% Total Hospitalized
  - 8% In-hospital Mortality

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**Selected Special Populations**
Andrew Skinner, M.D.

**Inflammatory Bowel Disease (IBD)**

- Ulcerative colitis (UC)
  - Underlying dysbiosis
  - 3.4% risk of CDI within 5 years
  - 33% more likely to suffer recurrent CDI when compared to persons without IBD
  - Combination of UC and CDI increase the risk of colectomy compared to persons without UC

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**Immunocompromised Status**

- **Solid organ transplant**
  - 5-fold increased rate of CDI
    - Higher risk with multi-organ transplant
    - Risk of recurrence is ~20% in solid organ transplant patients
- **Hematopoietic stem cell transplant**
  - Risk is 9-fold higher compared with general hospitalized patient
  - 1 in 10 allogeneic HSCT patients will have CDI


**Pediatric *C. difficile***

- **Infants**
  - Up to 60% colonized with *C. difficile* within the first year of life.
    - CDI is rare
  - 50% of newborns are colonized with toxigenic *C. difficile*
  - By age 3 years, children are colonized by *C. difficile* at rates similar to those in adults, 1 – 3%
    - Exceptions: Pediatric IBD and pediatric malignancies

Pediatric CDI

- Pediatric CDI has doubled over the past 2 decades
  - The incidence of pediatric CDI increased from 7.2 to 12.8 per 10,000 hospitalization
- From 2012 to 2016 pediatric CDI incidence increased from 24 to 35 per 100,000 patients
  - The majority are CA-CDI
- Paucity of treatment data until recently


Current and Emerging Pharmacologic and Non-Pharmacologic Therapies

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Prevention and Treatment of Recurrent *Clostridioides difficile* Infection

### Treatment Overview

**Currently approved therapies**
- Guideline recommendations
- Fidaxomicin updates
- Bezlotoxumab

**Emerging treatments**
- Antimicrobial agents
- Biotherapeutics

**Non-pharmacologic**
- Minimize risk factors
- Antimicrobial stewardship

### CDI Treatment Guidelines

- Clinical Practice Guidelines for *Clostridioides difficile* Infection in Adults and Children: 2017 Update by the Infectious Diseases Society of America (IDSA) and Society for Healthcare Epidemiology of America (SHEA)

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**Treatment of Initial Infection**

- **Non-severe:** WBCs <15,000 cells/mL, SCr <1.5 mg/dL
- **Severe:** WBCs ≥15,000 cells/mL, or SCr >1.5 mg/dL
- **Fulminant:** Hypotension or shock, ileus, megacolon

**Initial infection**

- Non-severe OR severe
  - **VAN** 125 mg orally 4 times/day x 10 days
  - **FDX** 200 mg orally twice daily x 10 days
  - Alternate if VAN/FDX unavailable: oral **MTZ** 500 mg 3 times/day x 10 days

- **Fulminant**
  - **VAN** 500 mg orally 4 times/day + **MTZ** 500 mg IV every 8 hours
  - If ileus: consider adding rectal VAN


**Treatment of Recurrent Infection**

- **First recurrence**
  - **MTZ** used for initial → **VAN** 125 mg orally 4 times/day x 10 days
  - **VAN** used for initial → **FDX** 200 mg orally twice daily x 10 days
  - **VAN** or **FDX** used for initial → prolonged tapered and pulsed oral **VAN** regimen
  - **VAN** orally in tapered and pulsed regimen

- **Second or subsequent recurrence**
  - **VAN** 125 mg orally 4 times/day x 10 days, then rifaximin 400 mg orally 3 times/day x 20 days
  - **FDX** 200 mg orally twice daily x 10 days
  - **FMT**

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**Pediatric CDI Recommendations**

- **Initial infection**
  - Non-severe: MTZ orally x 10 days, VAN orally x 10 days
  - Severe: Vancomycin (orally or rectally) with or without MTZ (IV) x 10 days

- **Recurrent Infection**
  - First recurrence, non-severe: MTZ orally x 10 days, VAN orally x 10 days
  - Second or subsequent recurrence: VAN in tapered and pulsed regimen
  - VAN x 10 days, then rifaximin x 20 days
  - FMT

**MTZ:** 7.5 mg/kg/dose (max 500 mg) three or four times/day
**VAN:** 10 mg/kg/dose (max 500 mg) four times/day


**Benefits of Fidaxomicin**

- Preservation of the intestinal microbiome during and after CDI treatment
- Prevents reappearance of stool toxin
  - Seen in 28% (26/94) of VAN-treated patients compared with 14% (13/91) of FDX-treated patients (P = 0.03)
- Adheres to *C. difficile* spores to inhibit germination and growth

Extended-pulsed Fidaxomicin (EPFX)

- EXTEND trial: randomized, controlled, open-label, superiority study

Hospitalized patients (age >60 years) with CDI (N=362)

Severity, Cancer, Age ≥75, Prior CDI episodes

FDX 200 mg BID (D1-5), then daily on alternate days (D7-25)

VAN 125 mg orally QID (D1-10)

Sustained clinical cure 30 days after EOT

D = day; EOT = end of treatment


EXTEND Trial Outcomes

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**Fidaxomicin SUNSHINE Trial**

- Randomized, investigator-blinded, non-inferiority study of fidaxomicin in children and adolescents

Patients aged <18 years with confirmed CDI (N=148)

<table>
<thead>
<tr>
<th>FDX x 10 days</th>
<th>Confirmed clinical response (CCR) at 2 days after EOT</th>
</tr>
</thead>
<tbody>
<tr>
<td>age &lt;6 yr: 16 mg/kg oral suspension BID [max 400 mg/d]; age ≥6 to &lt;18 yr: 200 mg tablets BID</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>VAN x 10 days</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>age &lt;6 yr: 10 mg/kg oral liquid QID [max 500 mg/d]; age ≥6 to &lt;18 yr: 125 mg capsules QID</td>
<td></td>
</tr>
</tbody>
</table>

**SUNSHINE Trial Outcomes**

<table>
<thead>
<tr>
<th></th>
<th>FDX (n=98)</th>
<th>VAN (n=44)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>CCR at 2 days after EOT</strong></td>
<td><img src="chart1.png" alt="Bar Chart" /></td>
<td><img src="chart2.png" alt="Bar Chart" /></td>
</tr>
<tr>
<td><strong>Global cure at EOS</strong></td>
<td><img src="chart3.png" alt="Bar Chart" /></td>
<td><img src="chart4.png" alt="Bar Chart" /></td>
</tr>
<tr>
<td><strong>Recurrence at EOS</strong></td>
<td><img src="chart5.png" alt="Bar Chart" /></td>
<td><img src="chart6.png" alt="Bar Chart" /></td>
</tr>
</tbody>
</table>

EOS = end of study, 30 days after EOT

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**Fidaxomicin for Pediatric Patients**

- New FDA-approved formulation: oral suspension
- New FDA-approved indication: treatment of CDI in children aged ≥6 months
  - Oral tablets (weight ≥12.5 kg and able to swallow tablets): 200 mg tablet BID x 10 days
  - Oral suspension (weight ≥4 kg): Weight-based dosing* BID x 10 days

*See package insert for full dosing recommendations.
Dificid (fidaxomicin) prescribing information. Merck & Co., Inc. 2020 Apr.

**Bezlotoxumab**

- Human monoclonal antibody that binds *C. difficile* toxin B
- Approved by FDA in June 2016
  - Secondary prevention of patients at high risk of rCDI who are receiving CDI treatment
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**MODIFY trials**

- Two double-blind, randomized, placebo-controlled phase 3 trials (MODIFY I & II)

**Participants with CDI recurrence**

<table>
<thead>
<tr>
<th></th>
<th>MODIFY I</th>
<th>MODIFY II</th>
<th>Pooled Data</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bezlotoxumab</td>
<td>67/386</td>
<td>62/395</td>
<td>129/781</td>
</tr>
<tr>
<td>Bezlotoxumab + Actoxumab</td>
<td>109/395</td>
<td>58/390</td>
<td>119/773</td>
</tr>
<tr>
<td>Placebo</td>
<td>60/232</td>
<td>97/370</td>
<td>206/773</td>
</tr>
<tr>
<td>Actoxumab</td>
<td>61/383</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*P*<0.001

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### Bezlotoxumab in High-Risk Patients

![Graph showing the reduction of recurrent *Clostridioides difficile* infection (rCDI) with bezlotoxumab compared to placebo in patients with different numbers of risk factors.](image)

- **No risk factor:** -15.9%*
- **≥1 risk factor:** -21.1%
- **1 risk factor:** -14.2%*
- **2 risk factors:** -14.2%*
- **3 risk factors:** -24.8%*

**Risk factors:**
- Age ≥65 years
- History of CDI in prior 6 months
- Immunocompromised
- Severe CDI
- Infection with CDI ribotype 027, 078, or 244

*P<0.05


### Bezlotoxumab Considerations

- Bezlotoxumab was associated with significantly lower rates of rCDI versus placebo
  - Patients with ≥3 risk factors had the greatest reduction of rCDI, but those with 1 or 2 risk factors also benefited

- Adverse reactions
  - Patients with heart failure experienced more adverse events & death with bezlotoxumab compared with placebo


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# Prevention and Treatment of Recurrent *Clostridioides difficile* Infection

## CDI Antimicrobial Pipeline

<table>
<thead>
<tr>
<th>Antibiotic</th>
<th>Mechanism of action</th>
<th>Formulation</th>
<th>Dose(s) under study</th>
<th>Clinical trials</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ridinilazole</td>
<td>Unknown</td>
<td>Oral capsule</td>
<td>200 mg twice daily x 10 days</td>
<td>Complete: Phase I, CoDIFy phase II Ongoing: Ri-CoDIFy phase III</td>
</tr>
<tr>
<td>LFF571</td>
<td>Elongation factor Tu (EF-Tu) inhibitor</td>
<td>Oral capsule</td>
<td>200 mg four times daily x 10 days</td>
<td>Complete: Phase I, Phase II</td>
</tr>
<tr>
<td>Ramoplanin</td>
<td>Peptidoglycan synthesis inhibitor</td>
<td>Oral</td>
<td>400 mg twice daily x 10 days</td>
<td>Complete: Phase I, Phase II</td>
</tr>
<tr>
<td>MGB-BP-3</td>
<td>Unknown</td>
<td>Oral</td>
<td>Unknown dose x 10 days</td>
<td>Complete: Phase I Ongoing: Phase II</td>
</tr>
<tr>
<td>DNV3837/DNV3681</td>
<td>Protein synthesis inhibitor (oxazolidinone-quinolone hybrid)</td>
<td>Intravenous solution</td>
<td>6 mg/kg infused at a rate of 0.5 mg/kg/hr over 12 hours x 10 days</td>
<td>Complete: Phase I Ongoing: Phase II</td>
</tr>
<tr>
<td>Ibezapolstat</td>
<td>DNA polymerase IIIC (pol IIIC) inhibitor</td>
<td>Oral capsule</td>
<td>450 mg twice daily x 10 days</td>
<td>Complete: Phase I Ongoing: Phase II</td>
</tr>
</tbody>
</table>

## CDI Biotherapeutic Pipeline

<table>
<thead>
<tr>
<th>Agent</th>
<th>Composition</th>
<th>Formulation</th>
<th>Dose(s) under study*</th>
<th>Clinical trials</th>
</tr>
</thead>
<tbody>
<tr>
<td>CP101</td>
<td>Lyophilized microbiota from human fecal donors</td>
<td>Oral capsule</td>
<td>1 capsule given one time</td>
<td>Complete: PRISM3 phase II Ongoing: PRISM-EXT phase II</td>
</tr>
<tr>
<td>RBX2660 &amp; RBX7455</td>
<td>RBX2660: Live bacterial suspension derived and standardized from human fecal donors RBX7455: Lyophilized oral formulation of RBX2660; stable at room temperature</td>
<td>Retention enema, Oral capsule</td>
<td>Unknown, Multiple doses for 2-4 days</td>
<td>RBX2660: Complete: PUNCH CD phase II, PUNCH CD 2 phase II, PUNCH Open Label phase II Ongoing: PUNCH CD3 phase III, PUNCH CD3-OLS phase III RBX7455: Complete: Phase I</td>
</tr>
<tr>
<td>SER-109</td>
<td>Firmicutes spores from healthy donor stool specimens (undefined consortium)</td>
<td>Oral capsule</td>
<td>4 capsules once daily for 3 days (phase III)</td>
<td>Complete: Phase Ib study, ECOSPOR phase II Ongoing: ECOSPORIII phase III, ECOSPORIV phase III</td>
</tr>
<tr>
<td>VE303</td>
<td>Clonal human commensal bacteria strains manufactured from clonal cell banks</td>
<td>Oral capsule</td>
<td>Multiple doses for 14 days</td>
<td>Complete: Phase I Ongoing: CONSORTIUM Phase II</td>
</tr>
</tbody>
</table>

*Following ≥10-14 days of SOC antibiotics

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Non-Pharmacologic Therapies

- Minimize modifiable host risk factors
- Diagnostic stewardship
- Infection prevention and control
  - Hand hygiene
  - Appropriate sterilization of healthcare facilities

The Role of Antimicrobial Stewardship

Implement antimicrobial stewardship programs (ASPs)
ASP implementation has been associated with a 52% risk reduction in CDI rate

Discontinue inciting antibiotic agent(s) as soon as possible
Continued antibiotic use is associated with decreases in clinical response rates and increases in CDI recurrence rates

Treat CDI for 10-day duration
May consider 14 days in patients with continued symptoms after 10 days of treatment

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**Key Takeaways**

- CDI is a microbiome-mediated disease
  - Treatment approaches should take impact on microbiome into consideration
- Pharmacists can help in the prevention of initial CDI and rCDI
  - Appropriate diagnostic testing and antimicrobial stewardship play key roles
- Future rCDI treatment and prevention strategies may look very different
  - Fidaxomicin results from EXTEND and SUNSHINE trials demonstrate benefit with novel dosing and in pediatric populations
  - Robust pipeline of antimicrobials and biotherapeutics in development

**Selected Resources**

- **CDC *C. difficile* Guidelines and Prevention Resources:**
  https://www.cdc.gov/cdiff/clinicians/resources.html
Consider these practice changes. Which will you make?

• Educate team members on factors that place patients at risk of recurrent CDI
• Educate team members on the emerging and current treatment options for managing patients with recurrent CDI
• Incorporate current evidence-based guidelines into practice when treating patients with recurrent CDI
• Collaborate with other healthcare professionals to formulate care plans for treating patients with recurrent CDI
• Collaborate with other healthcare professionals to develop strategies to prevent recurrent CDI